



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

OCT 17 1990 OCT 18 11:44

Craig Hammes  
Director, Regulatory Affairs  
Bayer Corporation  
Consumer Care Division  
P.O. Box 1910  
Morristown, New Jersey 17962-1910

Re: Docket No. 78N-0301  
Comments No. ANS3, LET12, C61, REF

Docket No. 78N-301F  
Comment No. C3

Dear Mr. Hammes:

Reference is made to comments submitted by Sterling Drug, Inc. on the use of a gel vehicle, as an alternative to light mineral oil, USP, as a liquid vehicle for a mixture containing 10.8 percent camphor and 4.7 percent phenol for general relief of pain and itch, and for relief of pain and/or itch of cold sores or fever blisters. This letter also concerns Sterling's data in support of the gel product for promotion of healing and for decreased healing time for fever blisters. Those data were submitted on January 25, 1983 in response to Dr. William Gilbertson's letter of December 17, 1982 regarding the advance notice of proposed rulemaking for over-the-counter (OTC) external analgesic drug products, published in the FEDERAL REGISTER of December 4, 1979 (44 FR 69768). The data are filed as Comment No. LET12, and Dr. Gilbertson's letter is filed as Comment No. ANS3 under Docket No. 78N-0301. Two other comments were submitted on April 7, 1983 and February 3, 1984 regarding the tentative final monograph for OTC external analgesic drug products, published in the FEDERAL REGISTER of February 8, 1983 (48 FR 5852). Those comments are filed as Comments No. C61 and REF, respectively, in the same docket. An additional comment, containing new data, was submitted on May 24, 1990 in relation to the tentative final monograph for OTC external analgesic drug products for the treatment of fever blisters and cold sores, published in the FEDERAL REGISTER of January 31, 1990 (55 FR 3370). The comment was filed as Comment No. C3 under Docket No. 78N-301F in the Dockets Management Branch.

Based on the information included in these various submissions, Sterling requested that the agency amend proposed § 348.20(a)(4) of the external analgesic drug products monograph to permit the use of a gel vehicle, as an alternative to light mineral oil, USP, as a liquid vehicle for a mixture containing 10.8 percent camphor and 4.7 percent phenol. The gel vehicle formulation expressed in percent weight/weight is as follows: eucalyptus oil

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0.4, colloidal silicon dioxide 5.0, glycerin 1.0, light mineral oil q.s. ad 100.0. The same formulation was tested in subjects as indicated in clinical trial data included in volumes 2 and 3 of comment no. C3. Sterling requested that the agency consider the new data to support the claim that camphor-phenol mixture using this gel as the vehicle promotes and quickens healing of fever blisters by treatment of herpes labialis in the prodromal (tingling/itching) or erythema stage.

In an October 11, 1995 telephone conversation with Mr. Michael Benson of my staff, Ms. Dina Russello of your company confirmed that Bayer Corporation is a successor-in-interest to Sterling's data and comments. The Division of OTC Drug Products has reviewed Sterling's comments and other information and determined that the gel vehicle described above is acceptable for use with a mixture containing 10.8 percent camphor and 4.7 percent phenol for general relief of pain and itch, and for relief of pain and/or itch of cold sores or fever blisters. However, we have determined that the data submitted do **not** support the indications for "promotion for healing" and "quickening of the healing time for fever blisters" for the camphor-phenol gel product.

We have the following specific comments concerning the information and data that Sterling submitted:

Camphor-Phenol Gel Suitability

The camphor-phenol liquid formulation has already been proposed as Category I with claims for: (1) temporary relief of minor skin wounds or irritations (§ 348.50(b)(2)), (2) temporary relief of pain and itching associated with cold sores (§ 348.50(b)(5)), and (3) as a first aid antiseptic to help prevent skin infection in minor wounds (§ 333.50(b)). The rulemakings for OTC external analgesic drug products and specifically for those products indicated for the treatment of fever blisters and cold sores, currently propose to restrict the vehicle for the camphor-phenol mixture to light mineral oil. All other vehicles were proposed as Category III. This decision was based in part on results of rabbit Draize tests showing that the liquid formulation had less eye irritancy than the gel formulation.

In response, Sterling filed data designed to demonstrate that irritancy is greatly reduced when the gel formulation is rinsed from the rabbit eye soon after instillation (Comment 61, Docket No. 78N-0301).

In addition, Sterling submitted the results of two ocular irritation studies which were performed on monkeys (Comment REF, Docket No. 78N-0301). In study #1, a two-phase study, 0.1 mL of the gel was instilled into one eye of two monkeys, and 0.05 mL of the gel was instilled into one eye of two other monkeys, with the contralateral eye serving as a control. The eyes were not washed after treatment in this first phase. Mild to moderate dose-related irritation (evaluated on the Draize scale) occurred, which resolved within 14 days. In the second phase, the previously untreated eyes were instilled with 0.05 mL of the camphor-phenol gel product and washed 4 seconds later with 20 mL of water. Slight transient conjunctival congestion was observed. Although this study used only 4 subjects, the trial was adequately done. Thus, the conclusion, that permanent ocular damage does not occur even if the product is not rinsed out, is valid.

In study #2, one eye of 9 monkeys was instilled with 0.1 mL of the gel product. Six of the treated eyes were unwashed and three were washed 4 to 5 seconds later. In the unwashed eyes, mild to moderate irritation cleared completely within 28 days. The irritation in the washed eyes was much milder and very transient in comparison (7 days). This study used more subjects, but still had nearly the same number of treated eyes. However, in all cases 0.1 mL was used, which was felt to be sufficient to mimic the worst case possible. We concluded that permanent ocular damage does not occur even if the product is not rinsed out to be valid.

These studies show that the instillation of the gel product into the eye results in moderate irritation which may not clear for several weeks unless the eye is rinsed immediately after exposure. If the latter is done, the irritation is very mild and transient. As a result of the burning sensation that would occur if the gel is inadvertently instilled into the eye, we believe that most consumers would most likely rinse the eye, thus minimizing the irritation.

The warning appearing on the Sterling product label is "Avoid using near eyes. If product gets into the eye, it should be washed out thoroughly with water and medical attention obtained." This warning is warranted in substance, however, a new format is required under 21 CFR 201.66, the final rule for format and content requirements for OTC drug product labeling published in the FEDERAL REGISTER of March 17, 1999 (64 FR 13254). In the new format, the warning would appear under the heading "Warnings," and under the subheading "When using this product," with a bullet

as a solid circle or square preceding the statement "do not use in or near eyes. If contact occurs, rinse eyes thoroughly with water." Accordingly, we plan to incorporate this warning into § 348.50(c) of the final monograph for OTC external analgesic drug products.

#### Treatment of Herpes Labialis with the Camphor-Phenol Gel

Sterling submitted a new clinical study in support of the efficacy of the new camphor-phenol gel product in relieving the pain and itching associated with *herpes labialis*, and in support of the product promoting healing and quickening the healing time if used beginning with the prodromal or erythema stage (Comment C3, vols. 1-3, Docket No. 78N-301F).

This study was conducted by Dr. James Leyden, Department of Dermatology, University of Pennsylvania, between June 15, 1988 and March 22, 1989. The study was designed to be double-blind, randomized, parallel, and vehicle-controlled. The protocol submitted with the report states that the patient population was to be healthy subjects 16 years of age or older. One hundred subjects enrolled and were instructed to apply a measured strip of gel to the cold sore lesions at the first sign or symptom in the prodromal or erythema stages. Therapy initiation was also allowed in the papule and vesicle stages, but not in the ulcer or crust stages.

Treatment was a 0.5 inch strip of active or vehicle-placebo gel applied four times a day during the waking hours for 14 days. Clinic visits were to be on study days 1, 2, 3, 4, 6, 8, 10, 14, 18, and 22 "as necessary until the lesion or lesions are healed." At each visit, pain, size, and lesion stage were to be noted. The duration of variables was to be timed from the onset of symptoms. For statistical data analysis, both parametric and non-parametric tests were proposed. Statistical significance was declared if  $p \leq 0.05$ .

According to the study report, 100 subjects were enrolled, 50 in each treatment group. The treatment groups were fairly well balanced for age and gender, but no information is available on prior history of *herpes labialis* or confirmation of diagnosis. Further, no attempt was made to determine whether the two groups were well balanced for lesion size at study entry. The study was apparently conducted in accordance with the protocol description, but both the protocol and the study report are sketchy when it comes to details of study conduct.

The investigator concluded that the gel product was statistically superior to placebo for pain intensity at visit 4 ( $p < 0.001$ ), visit 5 ( $p = 0.033$ ) and visit 7 ( $p = 0.007$ ); for pain relief at visit 1 ( $p < 0.001$ ) and visit 7 ( $p < 0.001$ ); for lesion size ( $p = 0.019$ ); for crust formation ( $p = 0.045$ ) and for healing time ( $p = 0.014$ ) in subjects with herpes labialis in the prodrome (tingling/itching) or erythema stage. No adverse experiences were reported and the gel was well tolerated by all subjects.

Review of the case report forms shows that 21 subjects reported a burning sensation immediately upon application (16 active treatment subjects and 5 placebo subjects). However, no visible irritation was noted, and the sensation did not persist.

We find that the study supports Sterling's claim of pain relief for this product, despite some concerns regarding blinding. The vehicle gel was identical to the active gel except for the phenol and camphor components, the latter has a distinctive smell and taste, not matched by the placebo which does not contain camphor and phenol and could not have the odors attributed to those two ingredients. Of note, camphor-phenol has already been accepted as an effective topical analgesic, and there is no evidence that the gel vehicle impairs the analgesic properties of the active ingredients.

We did not find the data supportive of the other parameters; i.e., significantly reduced lesion size, significantly shorter time to crust formation, and significantly quickened healing time. Sterling claimed that a significant reduction in lesion size was observed with active treatment on day 7, when compared to size on day 2. The study reported that the average reduction for the active group was 0.3776 mm compared to 0.2404 mm for the placebo group. Of note, lesion measurement techniques were imprecise. We consider the difference to be trivial and clinically insignificant.

We find no evidence that the ability of camphor and phenol to inactivate *herpes simplex* virus in vitro can be extrapolated to any antiviral activity in topical use in clinical disease. We find the evidence lacking to support accelerated healing.

An additional underlying problem with this study was that treatment may or may not have been initiated in the prodromal or erythema stages. Neither the protocol nor the study report explained how subjects were recruited or if medication was dispensed prospectively. Our review of the case report forms indicates that treatment was initiated in the vesicular stage in most subjects, though all reported prodromal symptoms. It is

appropriate to suggest use "at the first sign," but the study presented apparently did not initiate treatment in the prodromal stages. As a result, the study failed to show healing "speeded."

In conclusion, we find that the data support monograph classification of the camphor-phenol gel for a pain relief claim as described on p. 2 above, but not for a claim of accelerated healing. We are considering proposing that § 348.20(a)(4) be amended to read:

"Camphor and phenol identified in § 348.10(b)(3) and (8) may be combined in a light mineral oil, NF vehicle or in a gel vehicle with colloidal silicon dioxide; NF 5% w/w, eucalyptus oil 0.4% w/w, glycerin, USP 1% w/w in light mineral oil, NF q.s. ad 100% w/w."

In addition, as discussed above, in accordance with the format and content requirements for OTC drug product labeling in 21 CFR 201.66, we are considering proposing that the following warning for this product be included in the final monograph for OTC external analgesic drug products:

Under the heading "Warnings," and the subheading, "When using this product," [bullet] "do not use in or near the eyes. If contact occurs, rinse eyes thoroughly with water."

By letter dated October 12, 1995, Mr. Michael Kennedy, formerly with the Division of OTC Drug Evaluation informed your company of the need for a compendial monograph for the camphor-phenol complex before it is included in any final monograph. At the time that Sterling's data on the gel vehicle were submitted, the official compendia in effect were USP20/NF15. Glycerin, and light mineral oil were official in USP20, and eucalyptus oil and colloidal silicon dioxide were official in NF15. Currently, glycerin is official in USP24 and colloidal silicon dioxide and light mineral oil are official in NF19. Eucalyptus oil is no longer official in any of the compendia. Since the gel vehicle is a specific formulation that would be included in a final monograph, your company will also need to give attention to developing a compendial monograph for eucalyptus oil. Compendial monographs for the camphor-phenol complex and eucalyptus oil need your company's attention as soon as possible.

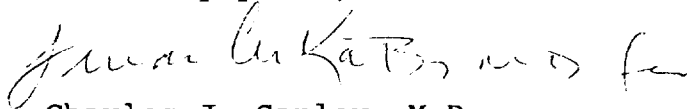
The Division of OTC Drug Products intends to recommend to the Commissioner that the agency respond to these comments in the above manner in the final monographs for OTC external analgesic drug products and OTC external analgesic drug products for the

Craig Hammes  
Bayer Corporation  
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treatment of fever blisters and cold sores, which will be published in future issues of the FEDERAL REGISTER. Following publication of the final rule for OTC external analgesic drug products for the treatment of fever blisters and cold sores, your company may file a citizen petition to amend the external analgesic final monograph with appropriate data to support the accelerated healing claim for the camphor-phenol gel. You may submit a protocol for a study to support this claim at any time. Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1061, 5630 Fishers Lane, Rockville, MD 20852.

We hope this information will be helpful.

Sincerely yours,

A handwritten signature in dark ink, appearing to read "Charles J. Ganley, M.D.", written in a cursive style.

Charles J. Ganley, M.D.  
Director  
Division of OTC Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: OCT 16 2000

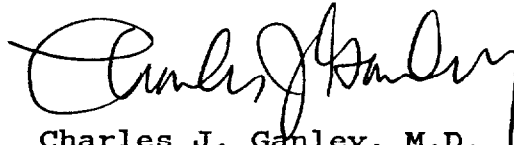
FROM: Director  
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 78N-0301

TO: Dockets Management Branch, HFA-305

☐ The attached material should be placed on public display under the above referenced Docket No.

☒ This material should be cross-referenced to  
Comment No. ANS 3, LET 12, C61

  
Charles J. Ganley, M.D.

Attachment